IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner: Yaen; Christopher H
Group Art Unit: 1642
Applicants: Eckert, Helmut et al.
Serial No.: 09/889,300
Filed: September 13, 2001
For: USE OF ANTIBODIES FOR THE VACCINATION AGAINST CANCER

Hon. Assistant Commissioner
For Patents
Washington, D.C. 20231

DECLARATION UNDER 37 C.F.R. § 1.132 of HANS LOIBNER

I, Hans Loibner, hereby declare and state as follows:

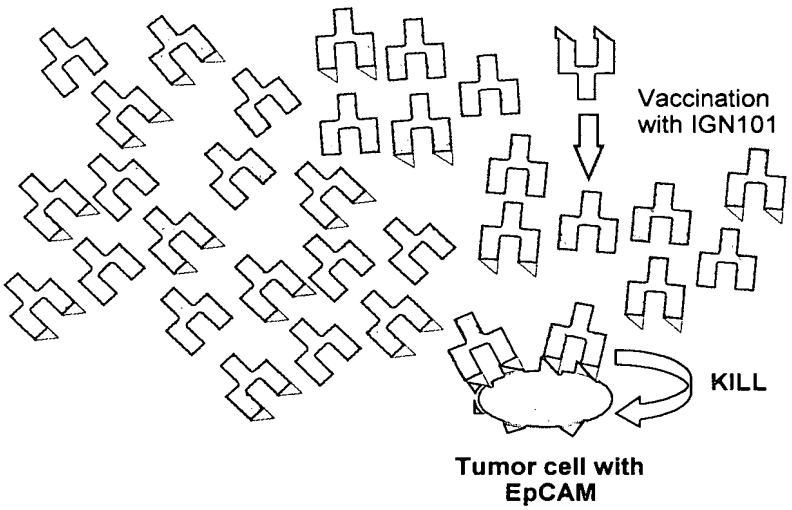
1. I am one of the co-inventors of the subject matter of the above-identified application.
2. I am currently Chief Executive Officer of Igeneon Krebs-Immuntherapie-Forschungs- und Entwicklungs-AG, a research based biotechnology company. Prior to that I was working as head of R&D of cancer vaccines for more than 15 years. My Curriculum Vitae is enclosed as Exhibit 1.
3. I have published over 15 scientific papers in the field of cancer research, a list of publications is enclosed as Exhibit 2.
4. I make this declaration to make record of supplemental results, which further demonstrate the safety and efficacy of a vaccine described in the above-identified application. Specifically I make this declaration to present the following clinical data derived from phase I and phase II clinical trials generated under my direction and supervision.
5. I declare that following description of clinical results includes safety, tolerability and efficacy of an anti-EpCAM antibody vaccine in treating cancer patients, wherein the patients are actively immunized by the anti-EpCAM antibody vaccine and the production of autologous antibodies can be actively induced thereby.

6. Mode of Action of the Vaccine:

IGN101 consists of a xenogeneic (foreign) protein used as vaccine antigen in an immunogenic formulation. This xenogeneic vaccine antigen is the murine monoclonal antibody 17-1A.
IGN101 has structural epitopes (mimotopes) related to EpCAM and elicits an immune response that is directed towards the vaccine antigen and because of its structural similarity, towards EpCAM.
Antibodies induced by vaccination with IGN101 recognize epithelial cancer cells as "foreign" and activate effector functions such as complement-dependent cytotoxicity (CDC) and antibody dependent cellular cytotoxicity (ADCC). These effector mechanisms may be directed to eliminate single carcinoma cells disseminated from the primary tumor.

EXHIBIT 4

Mechanism of action of IGN101



7. Summary of Clinical Trial Studies:

A **Phase I** clinical trial with IGN101 was completed at the Medical University Clinic Graz, Austria in 2001. 18 patients with biopsy proven carcinoma that failed conventional therapy or were deemed refractory to standard agents, were enrolled. Patients received 0.5 mg IGN101 subcutaneously on days 1, 15, 29 and 57.
Immunological assessments included the total humoral immune response, the IgG/IgM level and the amount of EpCAM specific antibodies. Evidence of anti-tumor effects were assessed by determination of the number of EpCAM positive tumor cells in blood measured on days 1, 29 and 71.

Phase I Results

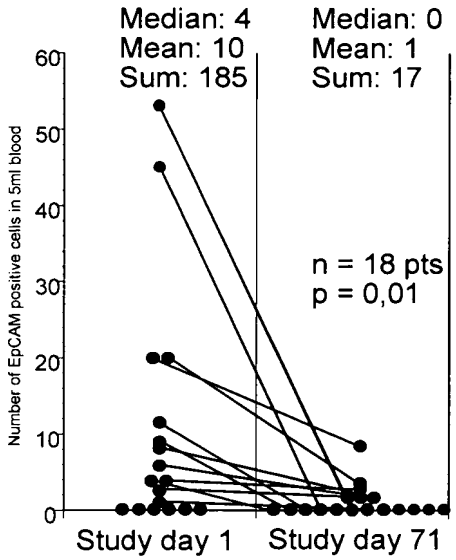
- **Excellent tolerability:** The only side effects seen were mild to moderate transient erythema (reddening of the skin) at the injection site, no systemic side effects were observed.

- **High overall and specific immunogenicity:** Seroconversion occurred in all patients and a secondary IgG antibody response was induced, indicating T-cell help and memory. In all patients anti-EpCAM IgG was induced. In 10/18 patients anti-EpCAM IgG 5-31 µg/ml serum was isolated.

- **No influence of prior chemotherapy (CT) on immunogenicity:** 12/18 patients received CT at least six weeks prior to vaccinations. These patients showed a similar overall and specific immune response compared to those without CT.

- **Early indication of efficacy:** The number of circulating EpCAM+ cells in blood significantly decreased during the vaccination course. Furthermore, in some patients a decrease or stabilization of tumor markers was seen. 15/18 patients showed stable disease for at least 2 months.

Figure 1: Reduction of EpCAM positive cells



Phase I:

18 cancer patients

4 vaccinations (d1, 15, 29, 57)

Assessment of circulating tumor cells in peripheral blood on days 1 and 71

A **Phase II** clinical trial was completed in 2002 at the Medical University Clinic Graz, Austria. Objective of the study was to assess the influence of concomitant chemotherapy (CT) on immunogenicity of IGN101 in patients with carcinoma likely to express EpCAM. Three different, frequently used CT regimens were analyzed. Results showed specific immunogenicity in almost all patients, comparable to results of Phase I, despite concomitant chemotherapy and no significant negative impact of the concomitant chemotherapy. The results allow further clinical testing of IGN101 in a wide range of clinical settings, including major cancer indications and stages where chemotherapy is standard of care.

Two Phase II studies and a Phase II/III study are currently under way. In an open-label Phase II study, IGN101 is being tested in 45 patients with epithelial cancers. Primary objective is assessment of surrogate efficacy of IGN101 against circulating tumor cells in blood. The study started in 2002 at the Medical University Clinic Graz, the University Clinic Innsbruck, the General Hospital (AKH) Vienna, Austria and the Charité, Berlin, Germany

Phase II efficacy trial

A placebo-controlled, double blind Phase II trial with IGN101 in 220 patients with three epithelial cancers (lung, colorectal, esophageal/gastric cancer) stage III and IV is currently being conducted. The study started in September 2001. Patient recruitment has ended beginning of July 2003. The study is performed under GCP rules and is expected to end in Q4 2003. The clinical end point is overall survival.

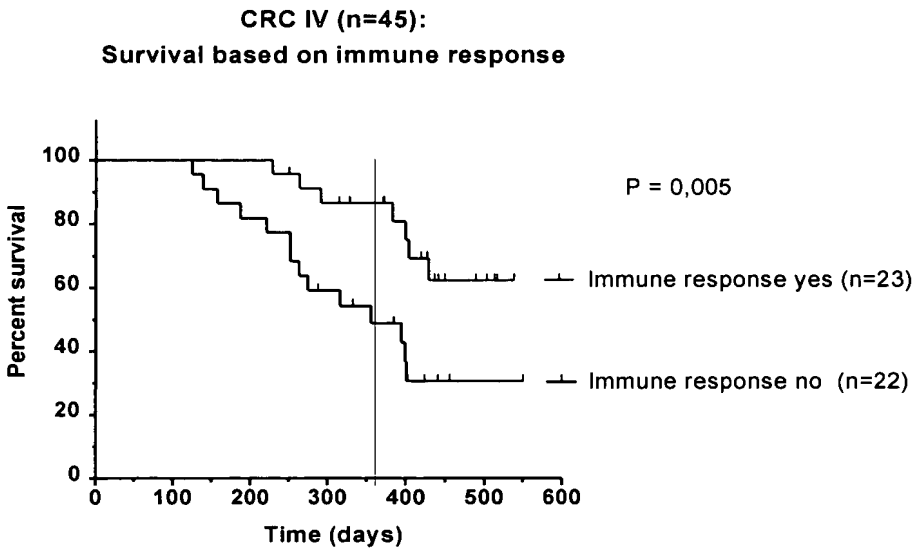
A blinded analysis of immune responses was performed with sera of 91 colorectal patients (45 in stage IV and 46 in stage III). 50.4% of these patients proved an immune response (50% is the theoretical number based on 1:1 randomization of placebo- and verum-treated patients).

Phase II Results

- **No influence of concomitant CT on immunogenicity:** In an open-label Phase II study, IGN101 was tested in 47 patients in direct combination with different chemotherapies to evaluate the influence of cytotoxic therapies on immunogenicity. Chemotherapy cycles started at the day of first vaccination and were continued as usual. Chemotherapies were grouped into taxane/anthracyclines, platinum compounds and others. As result, all patients mounted an immune response. A comparison of the immune responses with those observed in Phase I showed that overall and EpCAM-specific immunogenicity was mostly retained despite of different immunosuppressive CT.

- **Promising first survival benefit results:** In the context of the ongoing double blind placebo-controlled Phase II trial, a blinded analysis of immune responses was performed with sera of 91 colorectal patients (45 in stage IV and 46 in stage III). 50.4% of these patients proved an immune response to the vaccine antigen in IGN101 (50% is the theoretical number based on the 1:1 randomization of placebo- and IGN101-treated patients). The immune response results of the CRC stage IV patients were correlated with survival: The **1-year survival rate** of the CRC IV patients without immune response (n=22) is **45%**, corresponding well to the results of a large related database (Cochrane Library 2003, issue 1; 1-year survival 44.3%). The **1-year survival rate** of the CRC IV patients with a proven immune response to IGN101 (n=23) amounts to **85%**. This difference is statistically significant (p=0.005). The corresponding Kaplan-Meier survival curves are shown in figure 2. Patients in both groups are well balanced with regard to Karnofski performance status, liver enzyme values and treatment by concomitant chemotherapy.

Figure 2: Survival in M tastatic CRC (colorectal cancer)



8. I further declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of this application or any patent issuing thereon.

HANS LOIBNER; Ph.D.

Signed this 9 day of
September, 2003
At Vienna, Austria

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner: Yaen; Christopher H
Group Art Unit: 1642
Applicants: Eckert, Helmut et al.
Serial No.: 09/889,300
Filed: September 13, 2001
For: USE OF ANTIBODIES FOR THE VACCINATION AGAINST CANCER

Hon. Assistant Commissioner
For Patents
Washington, D.C. 20231

DECLARATION UNDER 37 C.F.R. § 1.132 of HANS LOIBNER

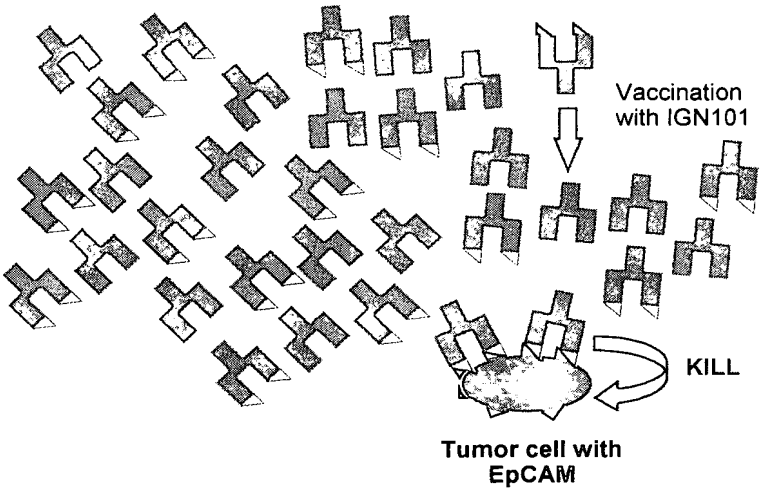
I, Hans Loibner, hereby declare and state as follows:

1. I am one of the co-inventors of the subject matter of the above-identified application.
2. I am currently Chief Executive Officer of Igeneon Krebs-Immuntherapie-Forschungs- und Entwicklungs-AG, a research based biotechnology company. Prior to that I was working as head of R&D of cancer vaccines for more than 15 years. My Curriculum Vitae is enclosed as Exhibit 1.
3. I have published over 15 scientific papers in the field of cancer research, a list of publications is enclosed as Exhibit 2.
4. I make this declaration to make record of supplemental results, which further demonstrate the safety and efficacy of a vaccine described in the above-identified application. Specifically I make this declaration to present the following clinical data derived from phase I and phase II clinical trials generated under my direction and supervision.
5. I declare that following description of clinical results includes safety, tolerability and efficacy of an anti-EpCAM antibody vaccine in treating cancer patients, wherein the patients are actively immunized by the anti-EpCAM antibody vaccine and the production of autologous antibodies can be actively induced thereby.

6. Mode of Action of the Vaccine:

IGN101 consists of a xenogeneic (foreign) protein used as vaccine antigen in an immunogenic formulation. This xenogeneic vaccine antigen is the murine monoclonal antibody 17-1A.
IGN101 has structural epitopes (mimotopes) related to EpCAM and elicits an immune response that is directed towards the vaccine antigen and because of its structural similarity, towards EpCAM.
Antibodies induced by vaccination with IGN101 recognize epithelial cancer cells as "foreign" and activate effector functions such as complement-dependent cytotoxicity (CDC) and antibody dependent cellular cytotoxicity (ADCC). These effector mechanisms may be directed to eliminate single carcinoma cells disseminated from the primary tumor.

Mechanism of action of IGN101



7. Summary of Clinical Trial Studies:

A **Phase I** clinical trial with IGN101 was completed at the Medical University Clinic Graz, Austria in 2001. 18 patients with biopsy proven carcinoma that failed conventional therapy or were deemed refractory to standard agents, were enrolled. Patients received 0.5 mg IGN101 subcutaneously on days 1, 15, 29 and 57.
Immunological assessments included the total humoral immune response, the IgG/IgM level and the amount of EpCAM specific antibodies. Evidence of anti-tumor effects were assessed by determination of the number of EpCAM positive tumor cells in blood measured on days 1, 29 and 71.

Phase I Results

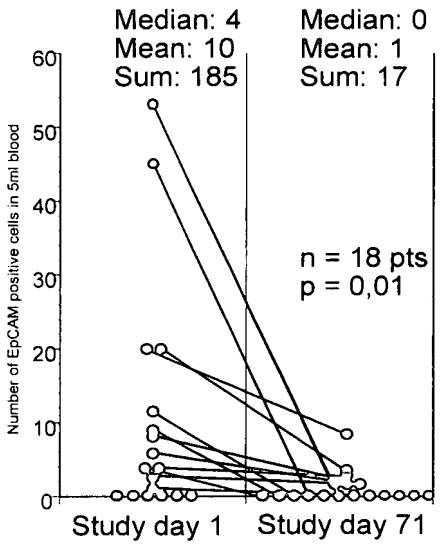
- **Excellent tolerability:** The only side effects seen were mild to moderate transient erythema (reddening of the skin) at the injection site, no systemic side effects were observed.

- **High overall and specific immunogenicity:** Seroconversion occurred in all patients and a secondary IgG antibody response was induced, indicating T-cell help and memory. In all patients anti-EpCAM IgG was induced. In 10/18 patients anti-EpCAM IgG 5-31 µg/ml serum was isolated.

- **No influence of prior chemotherapy (CT) on immunogenicity:** 12/18 patients received CT at least six weeks prior to vaccinations. These patients showed a similar overall and specific immune response compared to those without CT.

- **Early indication of efficacy:** The number of circulating EpCAM+ cells in blood significantly decreased during the vaccination course. Furthermore, in some patients a decrease or stabilization of tumor markers was seen. 15/18 patients showed stable disease for at least 2 months.

Figure 1: Reduction of EpCAM positive cells



Phase I:

18 cancer patients

4 vaccinations (d1, 15, 29, 57)

Assessment of circulating tumor cells in peripheral blood on days 1 and 71

A **Phase II** clinical trial was completed in 2002 at the Medical University Clinic Graz, Austria. Objective of the study was to assess the influence of concomitant chemotherapy (CT) on immunogenicity of IGN101 in patients with carcinoma likely to express EpCAM. Three different, frequently used CT regimens were analyzed. Results showed specific immunogenicity in almost all patients, comparable to results of Phase I, despite concomitant chemotherapy and no significant negative impact of the concomitant chemotherapy. The results allow further clinical testing of IGN101 in a wide range of clinical settings, including major cancer indications and stages where chemotherapy is standard of care.

Two Phase II studies and a Phase II/III study are currently under way. In an open-label Phase II study, IGN101 is being tested in 45 patients with epithelial cancers. Primary objective is assessment of surrogate efficacy of IGN101 against circulating tumor cells in blood. The study started in 2002 at the Medical University Clinic Graz, the University Clinic Innsbruck, the General Hospital (AKH) Vienna, Austria and the Charité, Berlin, Germany

Phase II efficacy trial

A placebo-controlled, double blind Phase II trial with IGN101 in 220 patients with three epithelial cancers (lung, colorectal, esophageal/gastric cancer) stage III and IV is currently being conducted. The study started in September 2001. Patient recruitment has ended beginning of July 2003. The study is performed under GCP rules and is expected to end in Q4 2003. The clinical end point is overall survival.

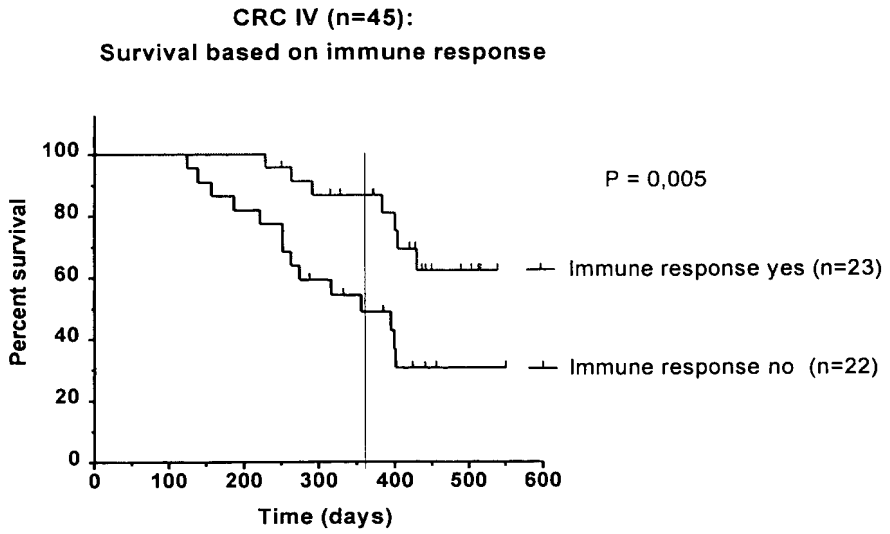
A blinded analysis of immune responses was performed with sera of 91 colorectal patients (45 in stage IV and 46 in stage III). 50.4% of these patients proved an immune response (50% is the theoretical number based on 1:1 randomization of placebo- and verum-treated patients).

Phase II Results

- **No influence of concomitant CT on immunogenicity:** In an open-label Phase II study, IGN101 was tested in 47 patients in direct combination with different chemotherapies to evaluate the influence of cytotoxic therapies on immunogenicity. Chemotherapy cycles started at the day of first vaccination and were continued as usual. Chemotherapies were grouped into taxane/anthracyclines, platinum compounds and others. As result, all patients mounted an immune response. A comparison of the immune responses with those observed in Phase I showed that overall and EpCAM-specific immunogenicity was mostly retained despite of different immunosuppressive CT.

- **Promising first survival benefit results:** In the context of the ongoing double blind placebo-controlled Phase II trial, a blinded analysis of immune responses was performed with sera of 91 colorectal patients (45 in stage IV and 46 in stage III). 50.4% of these patients proved an immune response to the vaccine antigen in IGN101 (50% is the theoretical number based on the 1:1 randomization of placebo- and IGN101-treated patients). The immune response results of the CRC stage IV patients were correlated with survival: The **1-year survival rate** of the CRC IV patients without immune response (n=22) is **45%**, corresponding well to the results of a large related database (Cochrane Library 2003, issue 1; 1-year survival 44.3%). The **1-year survival rate** of the CRC IV patients with a proven immune response to IGN101 (n=23) amounts to **85%**. This difference is statistically significant (p=0.005). The corresponding Kaplan-Meier survival curves are shown in figure 2. Patients in both groups are well balanced with regard to Karnofski performance status, liver enzyme values and treatment by concomitant chemotherapy.

Figure 2: Survival in Metastatic CRC (colorectal cancer)



8. I further declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of this application or any patent issuing thereon.

HANS LOIBNER; Ph.D.

Signed this 9 day of
September, 2003
At Vienna, Austria

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner: Yaen; Christopher H
Group Art Unit: 1642
Applicants: Eckert, Helmut et al.
Serial No.: 09/889,300
Filed: September 13, 2001
For: USE OF ANTIBODIES FOR THE VACCINATION AGAINST CANCER

Hon. Assistant Commissioner
For Patents
Washington, D.C. 20231

DECLARATION UNDER 37 C.F.R. § 1.132 of HANS LOIBNER

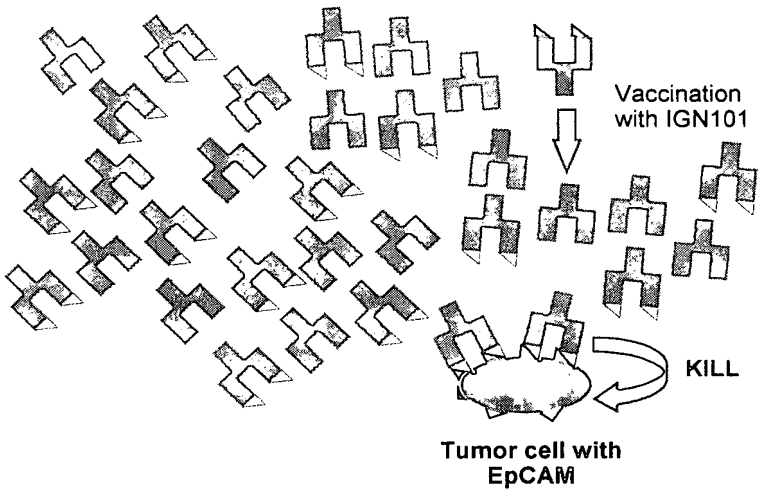
I, Hans Loibner, hereby declare and state as follows:

1. I am one of the co-inventors of the subject matter of the above-identified application.
2. I am currently Chief Executive Officer of Igeneon Krebs-Immuntherapie-Forschungs- und Entwicklungs-AG, a research based biotechnology company. Prior to that I was working as head of R&D of cancer vaccines for more than 15 years. My Curriculum Vitae is enclosed as Exhibit 1.
3. I have published over 15 scientific papers in the field of cancer research, a list of publications is enclosed as Exhibit 2.
4. I make this declaration to make record of supplemental results, which further demonstrate the safety and efficacy of a vaccine described in the above-identified application. Specifically I make this declaration to present the following clinical data derived from phase I and phase II clinical trials generated under my direction and supervision.
5. I declare that following description of clinical results includes safety, tolerability and efficacy of an anti-EpCAM antibody vaccine in treating cancer patients, wherein the patients are actively immunized by the anti-EpCAM antibody vaccine and the production of autologous antibodies can be actively induced thereby.

6. Mode of Action of the Vaccine:

IGN101 consists of a xenogeneic (foreign) protein used as vaccine antigen in an immunogenic formulation. This xenogeneic vaccine antigen is the murine monoclonal antibody 17-1A.
IGN101 has structural epitopes (mimotopes) related to EpCAM and elicits an immune response that is directed towards the vaccine antigen and because of its structural similarity, towards EpCAM.
Antibodies induced by vaccination with IGN101 recognize epithelial cancer cells as "foreign" and activate effector functions such as complement-dependent cytotoxicity (CDC) and antibody dependent cellular cytotoxicity (ADCC). These effector mechanisms may be directed to eliminate single carcinoma cells disseminated from the primary tumor.

Mechanism of action of IGN101



7. Summary of Clinical Trial Studies:

A **Phase I** clinical trial with IGN101 was completed at the Medical University Clinic Graz, Austria in 2001. 18 patients with biopsy proven carcinoma that failed conventional therapy or were deemed refractory to standard agents, were enrolled. Patients received 0.5 mg IGN101 subcutaneously on days 1, 15, 29 and 57.
Immunological assessments included the total humoral immune response, the IgG/IgM level and the amount of EpCAM specific antibodies. Evidence of anti-tumor effects were assessed by determination of the number of EpCAM positive tumor cells in blood measured on days 1, 29 and 71.

Phase I Results

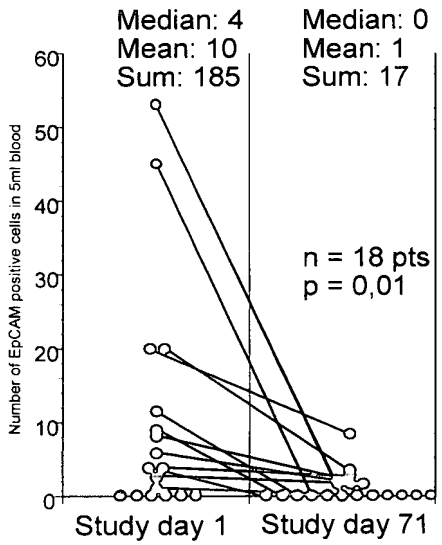
- **Excellent tolerability:** The only side effects seen were mild to moderate transient erythema (reddening of the skin) at the injection site, no systemic side effects were observed.

- **High overall and specific immunogenicity:** Seroconversion occurred in all patients and a secondary IgG antibody response was induced, indicating T-cell help and memory. In all patients anti-EpCAM IgG was induced. In 10/18 patients anti-EpCAM IgG 5-31 µg/ml serum was isolated.

- **No influence of prior chemotherapy (CT) on immunogenicity:** 12/18 patients received CT at least six weeks prior to vaccinations. These patients showed a similar overall and specific immune response compared to those without CT.

- **Early indication of efficacy:** The number of circulating EpCAM+ cells in blood significantly decreased during the vaccination course. Furthermore, in some patients a decrease or stabilization of tumor markers was seen. 15/18 patients showed stable disease for at least 2 months.

Figure 1: Reduction of EpCAM positive cells



Phase I:

18 cancer patients

4 vaccinations (d1, 15, 29, 57)

Assessment of circulating tumor cells in peripheral blood on days 1 and 71

A **Phase II** clinical trial was completed in 2002 at the Medical University Clinic Graz, Austria. Objective of the study was to assess the influence of concomitant chemotherapy (CT) on immunogenicity of IGN101 in patients with carcinoma likely to express EpCAM. Three different, frequently used CT regimens were analyzed. Results showed specific immunogenicity in almost all patients, comparable to results of Phase I, despite concomitant chemotherapy and no significant negative impact of the concomitant chemotherapy. The results allow further clinical testing of IGN101 in a wide range of clinical settings, including major cancer indications and stages where chemotherapy is standard of care.

Two Phase II studies and a Phase II/III study are currently under way. In an open-label Phase II study, IGN101 is being tested in 45 patients with epithelial cancers. Primary objective is assessment of surrogate efficacy of IGN101 against circulating tumor cells in blood. The study started in 2002 at the Medical University Clinic Graz, the University Clinic Innsbruck, the General Hospital (AKH) Vienna, Austria and the Charité, Berlin, Germany

Phase II efficacy trial

A placebo-controlled, double blind Phase II trial with IGN101 in 220 patients with three epithelial cancers (lung, colorectal, esophageal/gastric cancer) stage III and IV is currently being conducted. The study started in September 2001. Patient recruitment has ended beginning of July 2003. The study is performed under GCP rules and is expected to end in Q4 2003. The clinical end point is overall survival.

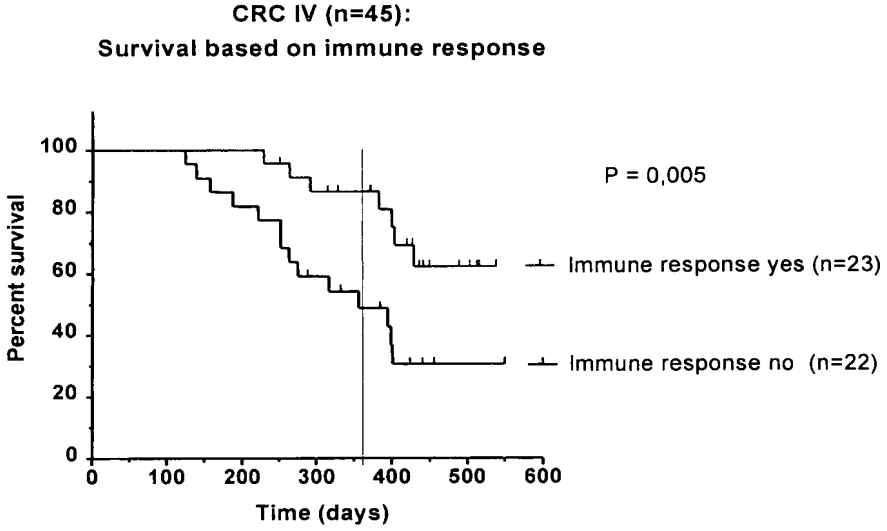
A blinded analysis of immune responses was performed with sera of 91 colorectal patients (45 in stage IV and 46 in stage III). 50.4% of these patients proved an immune response (50% is the theoretical number based on 1:1 randomization of placebo- and verum-treated patients).

Phase II Results

- **No influence of concomitant CT on immunogenicity:** In an open-label Phase II study, IGN101 was tested in 47 patients in direct combination with different chemotherapies to evaluate the influence of cytotoxic therapies on immunogenicity. Chemotherapy cycles started at the day of first vaccination and were continued as usual. Chemotherapies were grouped into taxane/anthracyclines, platinum compounds and others. As result, all patients mounted an immune response. A comparison of the immune responses with those observed in Phase I showed that overall and EpCAM-specific immunogenicity was mostly retained despite of different immunosuppressive CT.

- **Promising first survival benefit results:** In the context of the ongoing double blind placebo-controlled Phase II trial, a blinded analysis of immune responses was performed with sera of 91 colorectal patients (45 in stage IV and 46 in stage III). 50.4% of these patients proved an immune response to the vaccine antigen in IGN101 (50% is the theoretical number based on the 1:1 randomization of placebo- and IGN101-treated patients). The immune response results of the CRC stage IV patients were correlated with survival: The **1-year survival rate** of the CRC IV patients without immune response (n=22) is **45%**, corresponding well to the results of a large related database (Cochrane Library 2003, issue 1; 1-year survival 44.3%). The **1-year survival rate** of the CRC IV patients with a proven immune response to IGN101 (n=23) amounts to **85%**. This difference is statistically significant (p=0.005). The corresponding Kaplan-Meier survival curves are shown in figure 2. Patients in both groups are well balanced with regard to Karnofski performance status, liver enzyme values and treatment by concomitant chemotherapy.

Figure 2: Survival in Metastatic CRC (colorectal cancer)



8. I further declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of this application or any patent issuing thereon.

HANS LOIBNER; Ph.D.

Signed this 9 day of
September, 2003
At Vienna, Austria